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The Flavor and Fragrance High Production Volume Consortia

The Aromatic Consortium

Final Revised Robust Summaries for Phenethyl alcohol

Phenethyl alcohol **CAS No. 60-12-8**

FFHPVC Aromatic Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:
The Flavor and Fragrance High Production Volume Chemical Consortia
1620 I Street, NW, Suite 925
Washington, DC 20006
Phone: 202-331-2325
Fax: 202-463-8998

List of Member Companies

BASF

EASTMAN CHEMICAL COMPANY

FIRMENICH, INCORPORATED

GIVAUDAN CORPORATION

HAARMANN & REIMER CORPORATION

INTERNATIONAL FLAVOR & FRAGRANCES, INC.

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Robust Summaries for Phenethyl alcohol

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al*., 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1.Reliable without restrictions
- Reliability code 2.Reliable with restrictions
- Reliability code 3.Not reliable
- Reliability code 4.Not assignable

1 CHEMICAL AND PHYSICAL PROPERTIES

1.1 Melting Point

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Colorless liquid
Method/guideline	Measured
GLP	Ambiguous
Melting Point	-27 °C
Decomposition	No
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (1986) 67th edition, Robert C. Weast, editor, The Chemical Rubber Co Press, Inc. Boca Raton, FL.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Melting Point	-27 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc. Whitehouse Station, NJ.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/adapted Joback method
Melting Point	-6 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000a) US Environmental Protection Agency.

1.2 Boiling Point

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
GLP	Ambiguous
Boiling Point	218.2 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (1986) 67th edition, Robert C. Weast, editor, The Chemical Rubber Co Press, Inc. Boca Raton, FL.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Boiling Point	219 - 221 °C
Pressure	750 mm Hg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc. Whitehouse Station, NJ.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/adapted Stein and Brown method
Boiling Point	224.8 °C
Pressure	750 mm Hg
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000a) US Environmental Protection Agency.

1.3 Vapor Pressure

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
GLP	Ambiguous
Year	1995
Remarks for Test Conditions	Study was conducted at 30 °C, skin temperature
Vapor Pressure	0.0707 mm Hg
Temperature	30 °C

Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Vuilleumier C., Flament I., and Sauvegrain P. (1995) Headspace analysis study of evaporation rate of perfume ingredients applied to skin. Inter. J. of Cos. Sci., 17, 61-76.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Vapor Pressure	0.0868 mm Hg
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	MPBPVP EPI Suite (2000b) US Environmental Protection Agency (Daubert T.E. and Danner, R.P., 1989).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/modified Grain method
Vapor Pressure	0.0222 mm Hg
Temperature	25 °C
Remarks for Test Conditions	Based on input parameters: boiling point - 218.2 °C.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000a) US Environmental Protection Agency.

1.4 n-Octanol/Water Partition Coefficients

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Experimental

GLP	Not applicable
Log Pow	1.36
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Sangster J. (1989) Octanol-water partition coefficients of simple organic compounds. J Phys. Chem. Ref. Data, 18(3), 1111-1229.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Measured
Log Pow	1.36
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	KOWWIN EPI Suite (2000b) US Environmental Protection Agency (Hansch C. *et al*., 1995).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated/KOWWIN
Log Pow	1.57
Data Qualities Reliabilities	Reliability code 4. Not assignable
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000a) US Environmental Protection Agency.

1.5 Water Solubility

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/Guideline	Measured
Value (mg/L) at Temperature	22,200 mg/L at 25 °C

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	WSKOWIN EPI Suite (2000b) US Environmental Protection Agency (Vivandi S.C. *et al*., 1981)

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/Guideline	Measured
Value (mg/L) at Temperature	20,340 mg/L at ambient
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc. Whitehouse Station, NJ.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/Guideline	Calculated
Value (mg/L) at Temperature	32720 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWIN EPI Suite (2000a) US Environmental Protection Agency).

2 ENVIRONMENTAL FATE AND PATHWAYS

2.1 Photodegradation

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated
Test Type	AOPWIN
Halflife t1/2	12.6 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

2.2 Stability in Water

Substance Name	Phenethyl alcohol - No hydrolysis possible
CAS No.	60-12-8
Method/guideline	HENRYWIN
Test Type	SAR model
Halflife t1/2	Volatilization half-lives of 2529 hours from model river, and 27,680 days from model lake.
Data Qualities Reliabilities	Reliability code 4. Calculated
Remarks for Data Reliability	The data are obtained by a recognized SAR method and are consistent with chemical structure.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

2.3 Biodegradation

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	99.0% pure
Method	OECD Guideline 301B
Test Type	Sealed vessel carbon dioxide production test
GLP	Yes
Year	1994
Contact Time	28 days
Innoculum	Secondary effluent from an unacclimatized activated sludge plant at URL north.
Remarks for Test Conditions	Test material was directly added to the incubation mixture. The incubation was 28 days. The nominal concentration was 10 mg/l organic carbon. The test temperature range was 17-22 °C.
Degradation % After Time	106.3% after 28 days
Remarks Results	Biodegradation was 106.3% (103.3%-109.2%).
Time required for 10% degradation	1 day
10 day window criteria	Yes
Total degradation	Yes
Classification	Readily and ultimately biodegradable
Conclusion Remarks	Phenethyl alcohol was shown to be readily and ultimately biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Quest International Ltd. (1994) The ultimate biodegradability of phenylethyl alcohol in the sealed vessel test. Unpublished report.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated
Test Type	BIOWIN

Results	Probability of Rapid Biodegradation 1.03 (Linear Model) - 0.99 (Non-Linear). MITI Model 0.54 (Linear Model) - 0.71 (Non-Linear)
Conclusion Remarks	Expert Survey Biodegradation Results: Ultimate Survey Model: 3.0 (weeks) - Primary Survey 3.7 (days to weeks)
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

2.4 Fugacity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW=108 g/mole, VP=0.0868 mm Hg, log Kow=1.36, MP= -27 ^{o}C, BP= 218 ^{o}C water solubility=20,340 mg/L, Henry's LC
Media	Air
Model Data and Results	Half-life = 25.3 hours
Estimated Distribution and Media Concentration	2.3%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW=108 g/mole, VP=0.0868 mm Hg, log Kow=1.36, MP= -27 ^{o}C, BP= 218 ^{o}C water solubility=20,340 mg/L, Henry's LC
Media	Water
Model Data and Results	Half-life = 360 hours
Estimated Distribution and Media Concentration	46%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW=108 g/mole, VP=0.0868 mm Hg, log Kow=1.36, MP= -27 ^{o}C, BP= 218 ^{o}C water solubility=20,340 mg/L, Henry's LC
Media	Soil
Model Data and Results	Half-life = 360 hours
Estimated Distribution and	51.6%

Media Concentration	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Model Conditions	1000 kg/hr emissions
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III
Input Parameters	MW=108 g/mole, VP=0.0868 mm Hg, log Kow=1.36, MP= -27 ^{o}C, BP= 218 ^{o}C water solubility=20,340 mg/L, Henry's LC
Media	Sediment
Model Data and Results	Half-life = 1440 hours
Estimated Distribution and Media Concentration	0.09%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method.
References	Mackay D., A. DiGuardo, S. Paterson, G. Kicsi and C.E. Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A. DiGuardo, S. Paterson and C.E. Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

3 ECOTOXICITY

3.1 Acute Toxicity to Fish

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 99.5%
Method/guideline	DIN 38 412 96 hour static toxicity
Test Type	Experimental
GLP	No
Year	1988
Species/Strain/Supplier	Golden Orfe (*Leuciscus idus*)/
Exposure Period	96 hours
Analytical monitoring	None
Remarks for Test Conditions	Reconstituted fresh water according to guideline, 10 L at 21 °C. was purified by charcoal to remove chlorine and filtered (6 um). After 7 weeks adaptation, ten fish/concentration of body length 4.7 to 5.7 cm were exposed to 16 hours of daylight and 8 hours of darkness. Fish were observed at 0,3,6,24, 48, 72, and 96 hours. Initial test conditions were: pH=8.0; oxygen content, >60% of max; total hardness 2.5 mmoles; temperature=21 C. Loading was 3.7g fish/L. Positive control group was treated with chloroacetamide. Appropriate statistical analyses (Probit analysis) were performed according to Finney (1971).
Reference substances	Chloroacetamide -48 hour LC50=26 mg/L
Observations of Precipitation	No evidence of precipitation.
Endpoint value	LC50 = 220-460 mg/L
Nominal concentrations as mg/L	100, 215, 464, 1000 mg/L
Remarks fields for results	100% mortality at high dose after 1 hour and at 464 mg/L after 24 hour. No mortality at 2 lower concentrations. Test mortality data: 100 mg/L, 0/10 at all times; 215 mg/L, 0/10 at all time points; 464 mg/L, 8/10 at 4 hours and 10/10thereafter; 1000 mg/L 10/10 at all time points. Tumbling was seen in some animals at the 215 mg/L level. pH range, 7.7-8.0, oxygen content, 7.5-8.6, temperature 21 C
Unit	mg/L

Conclusion Remarks	LC50 =215 mg/L; NOAEL= 100 mg/L; LC100=464 mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	BASF AG (1988c) Abteilung Toxikologie unpublished data. (87/410).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	ECOSAR
Test Type	Calculated
GLP	Not Applicable
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Remarks for Test Conditions	Based on: melting point = -27 C; water solubility = 22,200 mg/L; KOW = 1.57.
Endpoint value	LC50 = 230 mg/L
Conclusion Remarks	LC50 = 230 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency, OPPT Risk Assessment Division (G. Cash & V. Nabholz, April 2001).

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 99%
Method/guideline	EPA EG1, 1982
Test Type	Experimental
GLP	No
Year	1988

Species/Strain/Supplier	*Daphnia magna Straus/* Institute National de Recherche Chimque Appliqee, France
Analytical procedures	None
Test Details	*Daphnia m*.were maintained on green algae and exposed to 16 hours of daylight (5 uEinstein) and 8 hours of darkness daily. The age of the Daphnia were 2-24 hours. Test were monitored at 0,3,6,24,and 48 hours. Initial test conditions were: pH=7.82; conductivity 640 uSiemens/cm); oxygen content 8.95-9.68 mg/L; total hardness 2.98 mmoles; temperature=292.1 K.
Nominal concentrations as mg/L	31.25, 62.5, 125,250, 500
EC50, EL50, LC0, at 24,48 hours	48 hour EC50 =287 (95% CI, 249 to 331.3 mg/L); 48 hour EC100=500 mg/L; 48 hour NOEL=125 mg/L
Conclusion remarks	The acute 48-hour EC50 for Daphnia m. with phenethyl alcohol is 287 mg/L and the 48 hour EC0=125 mg/L and EC100=500 mg/L
Biological observations	Animals swimming after 48 hours 20/20 at 31.25, 62.5, and 125 mg/L, 14/20 at 250 mg/L and 0/20 at 500 mg/L. pH range during test, 7.1-8.08. oxygen content during test 8.42-9.68
Appropriate statistical evaluations?	Yes
Data Qualities Reliabilities	Code 1. Guideline study.
Data Reliability Remarks	Reliability code 1. Reliable without restriction.
Reference	BASF AG (1988a) Labor Oekologie. Unpublished report (0107/88).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
Remarks for Test Conditions	Based on: melting point = -27 C; water solubility = 22,200 mg/L; KOW = 1.57.
EC50, EL50, LC0, at 24,48 hours	LC50 = 239 mg/L
Conclusion remarks	LC50 = 239 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.

Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency, OPPT Risk Assessment Division (G. Cash & V. Nabholz, April 2001).

3.3 Acute Toxicity to Aquatic Plants

Substance Name	Phenethyl alcohol (>99%)
CAS No.	60-12-8
Method/guideline	Experimental
Test Type	72 hour growth inhibition test
GLP	No
Year	1988
Species/Strain/Supplier	*Scenedesmus subspicatus subspicatus*
Exposure Period	72 hour
Nominal concentrations as mg/L	200, 280, 400, 560, 800, 1600
Remarks for Test Conditions	Algal solutions were maintained at pH=8.2 and 02 C. Light exposure was 10,000 Lux or 0.72 x 10^{20} photons/m^2 . Growth was measured at 24, 48, and 72 hours.
NOEC, LOEC or NOEL, LOEL	72 hour EC10=300 mg/L; EC50=490 mg/L; EC90=790 mg/L; NOEC 280 mg/L
Biological observations	Biomass
Conclusion Remarks	The 72-hour acute EC50 of phenethyl alcohol in *Daphnia m*=490 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report that meets basic scientific principles.
Reference	BASF AG (1988b) Labor Oekologie, Unpublished data (1010/88).

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Calculated
Test Type	ECOSAR
GLP	Not Applicable

Species/Strain/Supplier	Green algae
Exposure Period	96 hour
Remarks for Test Conditions	Based on: melting point = -27 C; water solubility = 22,200 mg/L; KOW = 1.57.
Endpoint value	EC50 = 146 mg/L
Conclusion Remarks	EC50 = 146 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency, OPPT Risk Assessment Division (G. Cash & V. Nabholz, April 2001).

4 HUMAN HEALTH TOXICITY

4.1 Acute Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks on Test Substance	Chemical Assay:>95%
Test Type	Acute oral LD50 study
GLP	Ambiguous
Year	1982
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5
Vehicle	0.25% methylcellulose
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Test material in 0.25% methylcellulose was given to groups of 10 (5/sex) Sprague-Dawley rats approximately 8 weeks of age at 1000, 1600, 2000, 2500 & 3200 mg/kg following an 18 hour fast. Animals were observed immediately and at 1, 4 & 24 hours after dose & 2 times/day for 14 days. LD50 with 95% confidence limits was determined by method of Litchfield and Wilcoxon (1949). Could not calculate the LD50 for females according to this method.
Value LD50 or LC50 with confidence limits	Male rat LD50 = 1692.9 mg/kg with 95% C.I. 1433.3-1998.9 mg/kg. Calculated LD50 for male and female rats = 1609 mg/kg 95% C.I. of 1399.6-1850.4 mg/kg.
Number of deaths at each dose level	1000 mg/kg: No deaths; 1600mg/kg: 5/10 dead; 2000 mg/kg: 9/10 dead; 2500 mg/kg: 10/10 dead. Clinical signs included diarrhea, decreased activity, piloerection, exophthalmus, ataxia, hyperactivity and hypersensitivity, chromodacryorrhea, tremors, wheezing and prostration. Necropsy revealed distended stomachs with hemorrhages of the glandular mucosa. Red foci on the thymus, discolored adrenals, and fluid-filled bladders were recorded.
Conclusion Remarks	The oral LD50 in male and female rats was reported to be 1609 mg/kg 95% C.I. of 1399.6-1850.4 mg/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	International Flavors & Fragrances, Inc. (1982) Acute oral toxicity study of phenethyl alcohol in rats. Unpublished report.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Rat
Sex	Not reported
Route of Administration	Oral
Value LD50 or LC50 with confidence limits	Reported LD50 = 2.46 ml/kg or 2509 mg/kg
Conclusion Remarks	The oral LD50 for phenethyl alcohol in rats was reported to be 2.46 (1.79-3.39) ml/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Published in a peer-reviewed journal.
References	Carpenter C.P., Weil, C.S., and Smyth, H.F. (1974) Range-finding toxicity data: List VIII. Toxicology and Applied Pharmacology, 28, 313-319.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1963
Species/strain	Rats/Osborne-Mendel
Sex	Male and Female
Route of Administration	Oral-Gavage
Value LD50 or LC50 with confidence limits	LD50 = 1790 mg/kg. 95% C.I. 1580-2020 mg/kg; Slope = 1.2 (1.1-1.3).
Number of deaths at each dose level	Death from 4 to 18 hours.

Remarks for Test Conditions	Animals were subjected to an 18-hour predose fast. All doses were given by intubation. The animals were observed over a 2-week period for mortality and/or systemic effects. LD50 results were calculated per Litchfield-Wilcoxon (1949). No necropsy mentioned
Remarks for Results	Toxic signs were coma within 15 minutes. Gross pathology showed irritation of the lower half of the stomach on the higher doses.
Conclusion Remarks	The oral LD50 in rats was calculated to be 1790 mg/kg. 95% C.I. 1580-2020 mg/kg; Slope = 1.2 (1.1-1.3). Study was conducted prior to GLP or OECD guidelines but was reported by respected researchers at the FDA and published in a peer-reviewed journal.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Published in a peer-reviewed journal.
References	Jenner P.M., Hagan, E.C., Taylor, J.M., Cook, E.L. and Fitzhugh, O.G. (1964) Food flavorings and compounds of related structure I. Acute oral toxicity. Food and Cosmetics Toxicology, 2(3), 327-343.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	Ambiguous
Year	1982
Species/strain	Rat/Wistar
Sex	Male
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral
Remarks for Test Conditions	Animals were observed for 14 days.
Value LD50 or LC50 with confidence limits	Reported LD50 = 1500 mg/kg (C.I. 1200-2000 mg/kg)
Number of deaths at each dose level	Dose 760 mg/kg: 1/10 dead; 1200 mg/kg: 1/10 dead; 1900 mg/kg: 9/10 1.9 dead; 5000 mg/kg: 10/10 dead.
Conclusion remarks	The oral LD50 for phenethyl alcohol was calculated to be 1500 mg/kg (C.I. 1200 - 2000 mg/kg) in rats.

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Moreno O. M. (1982a) Acute toxicity studies. Unpublished report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Rat
Sex	Male and Female
# of Animals per Sex per Dose	6 males and 5 females
Vehicle	Sunflower oil
Route of Administration	Oral-Gavage
Remarks for Test Conditions	15-day observation period. Vehicle was sunflower oil.
Value LD50 or LC50 with confidence limits	Reported LD50 = 2540 mg/kg
Conclusion Remarks	The acute oral LD50 in rats was reported to be 2540 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Zaitsev A.N. and Rakhmanina, N.L. (1974) Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vop. Pitan, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Mice
Sex	Male and Female

# of animals per sex per dose	6 males and 5 females
Vehicle	Sunflower oil
Route of Administration	Oral-Gavage
Remarks for Test Conditions	15-day observation period. Vehicle was sunflower oil.
Value LD50 or LC50 with confidence limits	Reported LD50 = 2540 mg/kg.
Conclusion Remarks	The acute oral LD50 in mice was reported to be 2540 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Data Reliabilities Remarks	Code 3. Documentation insufficient for assessment.
References	Zaitsev A.N. and Rakhmanina, N.L. (1974) Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vop. Pitan, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1963
Species/strain	Mice
Sex	Not reported
Route of Administration	Oral
Remarks for Test Conditions	Not reported
Value LD50 or LC50 with confidence limits	Reported LD50 = 800 -1500 mg/kg
Number of deaths at each dose level	Not reported
Conclusion Remarks	The acute oral LD50 in mice was reported to be 800 -1500 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1974
Species/strain	Guinea pig
Sex	Male and Female
# of animals per sex per dose	6 males and 5 females
Route of Administration	Oral-Gavage
Vehicle	Sunflower oil
Value LD50 or LC50 with confidence limits	Reported LD50 = 2540 mg/kg
Remarks for test conditions	15-day observation period. Vehicle was sunflower oil.
Conclusion Remarks	The acute oral LD50 in guinea pig was reported to be 2540 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Zaitsev A.N. and Rakhmanina, N.L. (1974) Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vop. Pitan, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute oral LD50 study
GLP	No
Year	1963
Species/strain	Guinea pig
Sex	Not reported
# of animals per sex per dose	Not reported
Route of Administration	Oral

Vehicle	Not reported
Value LD50 or LC50 with confidence limits	Calculated LD50 = 400 - 800 mg/kg
Conclusion Remarks	The acute oral LD50 value in guinea pig was calculated to be 400 - 800 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute dermal LD50 study
GLP	No
Year	1974
Species/strain	Rabbit
Sex	Not reported
Route of Administration	Dermal
Value LD50 or LC50 with confidence limits	Reported LD50 = 0.79 ml/kg or 805 mg/kg
Conclusion Remarks	The dermal LD50 for phenethyl alcohol in rabbits was reported to be 0.79 ml/kg (0.49-1.30) ml/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliabilities Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Published in a peer-reviewed journal.
References	Carpenter C.P., Weil, C.S., and Smyth, H.F. (1974) Range-finding toxicity data: List VIII. Toxicology and Applied Pharmacology, 28, 313-319.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute dermal LD50 study
GLP	Yes
Year	1982
Species/strain	Rat/ male albino

Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Dermal
Remarks for Test Conditions	5000 mg/kg was applied to the rat skin
Value LD50 or LC50 with confidence limits	LD50 greater than 5000 mg/kg
Number of deaths at each dose level-other effects	Number of deaths: 5000 mg/kg, 0/10. Skin reactions were absent. At necropsy, no gross lesions to organs were recorded.
Conclusion Remarks	The dermal LD50 in rat was reported to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Moreno O. M. (1982b) Acute toxicity studied. Unpublished report to RIFM.

Substance Name	Phenethyl alcohol (Assay: >95%)
CAS No.	60-12-8
Test Type	Acute dermal LD50 study
GLP	Ambiguous
Year	1983
Species/strain	Rabbits/New Zealand white
Sex	Male and Female
# of animals per sex per dose	4
Route of Administration	Dermal
Value LD50 or LC50 with confidence limits	LD50 = 2535 mg/kg (C.I. 1769-3634 mg/kg).
Remarks for Test Conditions	Test material at 1600, 2500 and 4000 mg/kg was applied to abraded and intact skin of groups of 8 (4/sex) New Zealand white rabbits. Rabbits weighed between 2 and 3 kg at initiation of the study. Test sites were washed after 24 hours. Observations recorded 2 & 4 hour later & twice daily thereafter for 14 days. Necropsy of animals dying on study included hemorrhages in the muscle at the application site and dark fluid in the bladder. Also recorded were distended stomachs and intestines, fluid in the abdominal cavity, and hemorrhages of the caecum and pale kidneys.
Number of deaths at each	1600 mg/kg: 1/8 died; 2500 mg/kg: 5/8 died; 4000 mg/kg: 6/8

dose level	died.
Conclusion Remarks	The acute dermal LD50 value in rabbits was calculated to be 2535 mg/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	International Flavors & Fragrances, Inc. (1983) Acute dermal toxicity test of phenethyl alcohol in rabbits. Unpublished report.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute intraperitoneal LD50 study
GLP	No
Year	1963
Species/strain	Mice
Sex	Not reported
# of animals per sex per dose	Not reported
Route of Administration	Intraperitoneal
Value LD50 or LC50 with confidence limits	Reported LD50 = 200 - 400 mg/kg
Conclusion Remarks	The intraperitoneal LD50 value in mice was reported to be 200 - 400 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute intraperitoneal LD50 study
GLP	No
Year	1963
Species/strain	Guinea pig
Sex	Not reported

# of animals per sex per dose	Not reported
Route of Administration	Intraperitoneal
Value LD50 or LC50 with confidence limits	Calculated LD50 = 400 - 800 mg/kg
Conclusion Remarks	The intraperitoneal LD50 in guinea pig was calculated to be 400 - 800 mg/kg.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Fassett D.W. (1963) Personal communication. In Industrial Hygiene and Toxicology, 1476-1477.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Acute inhalation LC50 study.
GLP	Ambiguous
Year	1980
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5
Vehicle	Aerosol
Route of Administration	Inhalation
Remarks for Test Conditions	After a 4-hour exposure the following observations were made over a 14-day period: mortality, clinical signs, body weight, gross and histopathology.
Value LD50 or LC50 with confidence limits	Acute inhalation LC50 was reported to be greater than 4.63 mg/L.
Number of deaths at each dose level	0/10 at 4.63 mg/L
Remarks for Results	The animals exhibited no clinical signs during or up to 14 days after exposure at 4.63 mg/L.
Conclusion Remarks	Acute inhalation LC50 for phenethyl alcohol in rats was reported to be greater than 4.63 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Breckenridge C., C.J.Collins, S.Qureshi and B.G.Procter (1980) The acute toxicity of inhaled phenyl ethyl alcohol in the albino

rat. Unpublished report to RIFM.

4.2 Genetic Toxicity

4.2.1 *In vitro* genotoxicity

Substance Name	Phenethyl alcohol, 2-methyl
CAS No.	1123-85-9
Remarks for Test Substance	Surrogate data for phenethyl alcohol
Method/guideline	Ames test was performed on five tester strains of Salmonella typhimurium TA 1535, TA 100, TA 1537, TA 1538, TA 98.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	NG
Year	1983
Species/Strain	Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 1538, TA 98.
Metabolic Activation	S-9 liver fraction was prepared from Aroclor-pretreated rats (Aroclor 1254, 500 mg/kg, ip).
Doses/Concentration	5 concentrations up to 3600 ug/plate (toxicity >3600 ug/plate)
Statistical Methods	Statistical significance was determined according to the methods of Kastenbaum and Bowman (1970).
Remarks for Test Conditions	A two-fold elevation in revertants for the test material over controls was considered a positive response. Positive controls were run in each experiment with the reference mutagens sodium azide and benzo[a]pyrene. Number of revertants per plate for positive controls: Sodium azide (0.5 ug/plate): TA1535, 430-760 and TA100, 400-700 Benzopyrene (5 ug/plate): TA100, 865-1210, TA1537, 410-590 and TA1538, 660-1000 Test material was applied neat. Experiments were performed in duplicate at all concentrations in all five tester strains.
Results	No mutagenic activity was detected with any of the Salmonella strains tested.
Cytotoxic concentration	>3600 µg/plate
Genotoxic effects	None
Conclusion Remarks	No mutagenic activity was detected with any of the Salmonella

	strains tested.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Wild D., King, M.T., Gocke, E. and Eckhardt. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus tests Food and Chemical Toxicology 21(6), 707-719.
Substance Name	Phenylacetic acid
CAS No.	103-82-2
Remarks for Test Substance	Surrogate data for phenethyl alcohol. Phenylacetic acid is predominant metabolite of phenethyl alcohol present in vivo.
Method/guideline	Ames assay (Ames et al., 1973; McCann et al., 1975)
Test Type	Reverse mutation assay
System of Testing	Bacterial
GLP	NG
Year	1989
Species/Strain	Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Metabolic Activation	S9 fraction of Aroclor 1254-induced Sprague-Dawley rat liver
Doses/Concentration	14 concentrations from 1.22 to 10,000 ug/plate
Remarks for Test Conditions	Bacteria were culture in Oxford medium #2 for 12 hours. Assays were conducted by addition of 2.0 ml of test article to agar along with 0.1 ml of bacterial culture and either metabolic activation mix or an equivalent volume of phosphate buffer. The mixture was incubated for 48 hours and revertant colonies counted. Experiments were run in triplicate. Solvent control was DMSO and positive controls were sodium azide (10 µg/plate) for TA 1535 and TA100, 2-nirofluorene (10 µg/plate) for TA 1538 and TA 98, and 9-aminoacridine (50 µg/plate) for TA1537.
Results	No increase in reverse mutations, with or without S9 mix.
Cytotoxic concentration	Highest dose level selected (10,000 µg/plate) exhibited 100% toxicity
Genotoxic effects	None reported
Conclusion Remarks	Phenylacetic acid was not mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Heck, J.D., T.A. Vollmuth, M.A. Cifone, D.R. Jagannath, B. Myhr and R.D. Curren (1989). An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The

Toxicologist 9(1): 257.

Substance Name	Phenylacetic acid
CAS No.	103-82-2
Remarks for Test Substance	Surrogate data for phenethyl alcohol. Phenylacetic acid is predominant metabolite of phenethyl alcohol present in vivo.
Method/guideline	Mouse lymphoma assay (Clive et al., 1979)
Test Type	Mammalian mutation assay
System of Testing	Mouse lymphoma cell
GLP	NG
Year	1989
Species/Strain	L5178Y mouse lymphoma cell
Metabolic Activation	Induced rat liver S9 and cofactors
Doses/Concentration	Five test concentrations from 31.3 to 500 ug/ml
Remarks for Test Conditions	Thymidine kinase competent heterozygote was exposed to the test article in the presence or absence of S9. After a 4-hour exposure, cells were washed, incubated (48hrs) to allow phenotypic expression, and colonies were counted after 10-14 days growth. Mutant frequency calculated using the ratio of mutant to viable colonies cloned without selective medium.
Results	Negative at 500 µg/mL with and without S9.
Cytotoxic concentration	Lethal concentration 1000 µg/ml
Genotoxic effects	None reported
Conclusion Remarks	Phenylacetic acid was not mutagenic in the presence or absence of metabolic activation.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Heck, J.D., T.A. Vollmuth, M.A. Cifone, D.R. Jagannath, B. Myhr and R.D. Curren (1989). An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist 9(1): 257.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 97%
Method/guideline	Ames test

Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	*Salmonella typhimurium* strains TA98, TA100, TA1535 & TA1537
Metabolic Activation	With and without S9 fraction rat liver treated with Aroclor 1254
Doses/Concentration	3 micromole/plate (366 µg/plate)
Statistical Methods	Not given
Remarks for Test Conditions	The solvent used was ethanol. Only one replicate was performed for the substances, which tested negative. Similar to OECD 471. No *E. coli* strain was included.
Results	No effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate Statistical Evaluations	None given
Conclusion Remarks	No mutagenic activity of phenethyl alcohol was observed using *Salmonella typhimurium* strains TA98, TA100, TA1535 & TA153 in the presence or absence of S9 fraction.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Study was a single concentration screening test. No assessment of cytotoxicity was performed.
References	Florin I., Rutberg, L., Curvall, M. and Enzell, C. R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology, 18, 219-232.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity greater than 98%
Method/guideline	*In Vitro* Chromosome Aberration Test with Human Lymphocytes
Test Type	Sister Chromatid Exchange
System of Testing	Human lymphocytes
GLP	No
Year	1983

Species/Strain	Adult male human whole-blood lymphocytes
Metabolic Activation	None
Doses/Concentration	0.1, 0.5, 1, 5 & 10 mM
Statistical Methods	t-test
Remarks for Test Conditions	Vehicle was acetone. Time between treatment and harvest was 48 hours. Entire culture time was 72 hours with colcemid present in the culture for 2.5 hours
Results	No effects
Cytotoxic concentration	Approximately 5 mM
Genotoxic Effects	None
Appropriate statistical evaluations?	Yes
Conclusion Remarks	Phenethyl alcohol was unable to induce Sister-Chromatid Exchange in whole-blood lymphocyte cultures of a healthy male donor.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Norppa H. and Vainio, H. (1983) Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. Mutation Research, 116, 379-387.

Substance Name	Phenylacetic acid
CAS No.	103-82-2
Remarks for Substance	Surrogate data for phenethyl alcohol. Phenylacetic acid is predominant metabolite of phenethyl alcohol present in vivo.
Method/guideline	Unscheduled DNA Synthesis Assay (UDS)
Test Type	Unscheduled DNA synthesis
System of Testing	Rat hepatocytes
GLP	Not given
Year	1989
Species/Strain	Rat/Fischer and Sprague-Dawley adult male
Metabolic Activation	No
Doses/Concentration	1500 micrograms
Statistical Methods	Not given

Remarks for Test Conditions	Livers were perfused *in situ* with 0.5 mM EDTA in HEPES buffer (pH 7.2) for four minutes. Cultures of rat liver hepatocytes were incubated with the test material for 18-20 hours. UDS was measures by electronically counting nuclear grains and subtracting the average number of grains in 3 adjacent nuclear-sized cytoplasmic areas. 75-150 cells were analyzed for each dose level. The test was considered positive if an increase in net nuclear grain counts of at least six grains per nucleus above the solvent control and/or an increase in the percent of nuclei with at least 6 net grains to more than 10% above the negative control value.
Results	Negative at all dose levels
Cytotoxic concentration	Non-toxic at all dose levels
Genotoxic Effects	None
Appropriate statistical evaluations?	Not given
Remarks for results	The test article did not cause a significant increase in UDS as measured by the mean number of net nuclear grain counts by any dose level. The positive control, 7,12-dimethylbenz(a)-anthracene (DMBA), induced significant increases in the mean number of net nuclear grain counts compared to the solvent control.
Conclusion Remarks	There was no increase in unscheduled DNA synthesis.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Heck J. D., Vollmuth, T. A., Cifone, M. A., Jagannath, D. R., Myhr B., and R.D. Curren (1989) An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist, 9(1), 257.

4.2.2 *In vivo* Genotoxicity

Substance Name	Phenylacetaldehyde, 2-methyl
CAS No.	93-53-8
Remarks for Substance	Surrogate data for phenethyl alcohol
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler *et al*., 1977)
Test Type	Lethal mutation test
GLP	Ambiguous
Year	1983

Species/Strain	*Drosophila melanogaster*
Sex	Not reported
Route of Administration	Oral-Diet
Doses/Concentration	10 mM
Exposure Period	Not reported
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Approximately 1200 X-chromosomes were tested per experiment in three successively broods. F2 progeny culture with 2 or fewer wild-type males were routinely tested in the F3 generation to confirm X-linked recessive lethal mutations. Basc test protocol as described in Wurgler et al., 1977) was used. Test concentrations were selected to be slightly less than the LD50 for the substance (E.Gocke, M.-T.King, K.Eckhardt and D.Wild (1980) Mutation Research, 90, 91-109).
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Number of sex-linked lethal/chromosomes tested in Brood 1, 3/1187(0.25%). Brood II, 2/650 (0.31%), and Brood III, 2/1180 (0.17%). Control%: Brood 1, (0.23%). Brood II, (0.19%), and Brood III, (0.29%)
Genotoxic effects	None
Remarks for Results	Ten mM solutions of phenylacetaldehyde, 2-methyl did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion Remarks	10 mM solutions of phenylacetaldehyde, 2-methyl did not induce sex linked recessive lethals in *Drosophila melanogaster*.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

Substance Name	Isooeugenyl phenylacetate
CAS No.	120-24-1
Remarks for Substance	Data for phenyacetic acid ester, isoeugenol phenylacetate. Based on anticipated hydrolysis of ester, phenylacetic acid is formed in vivo. Phenylacetic acid is the predominant metabolite of phenethyl alcohol.

Method/guideline	Sex linked recessive lethal mutation assay (Wuergler *et al*., 1977)
Test Type	Lethal mutation test
GLP	Ambiguous
Year	1983
Species/Strain	*Drosophila melanogaster*
Sex	Not reported
Route of Administration	Oral-Diet
Doses/Concentration	25 mM
Exposure Period	Not reported
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Approximately 1200 X-chromosomes were tested per experiment in three successively broods. F2 progeny culture with 2 or fewer wild-type males were routinely tested in the F3 generation to confirm X-linked recessive lethal mutations. Basc test protocol as described in Wurgler et al., 1977) was used. Test concentrations were selected to be slightly less than the LD50 for the substance (E.Gocke, M.-T.King, K.Eckhardt and D.Wild (1980) Mutation Research, 90, 91-109).
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Number of sex-linked lethal/chromosomes tested in Brood 1, 6/1223 (0.41%). Brood II, 2/1097 (0.18%), and Brood III, 1/1200 (0.08%). Control%: Brood 1, (0.23%). Brood II, (0.19%), and Brood III, (0.29%)
Genotoxic effects	None
Remarks for Results	Twenty-five mM solutions of phenylacetic acid, isoeugenol ester did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion Remarks	Phenylacetic acid, isoeugenol ester did not induce sex linked recessive lethals in Drosophila melanogaster.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

Substance Name	Phenylacetaldehyde, 2-methyl
CAS No.	93-53-8
Remarks for Substance	Surrogate data for phenethyl alcohol
Method/guideline	Micronucleus test
Test Type	Clastogenic assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	134, 402, or 670 mg/kg bw in olive oil
Exposure Period	One dose at 0 hours
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 hours with 134, 402, or 670 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976). The intraperitoneal LD50>800 mg/kg. Positive control as specified in previous publication (Eckhardt et al., 1980)
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 134, 402, and 670 mg/kg bw was 1.5, 2.3, 1.3, and 2.5, respectively
Genotoxic effects	None
Conclusion Remarks	Phenylacetaldehyde, 2-methyl did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

Substance Name	Isooeugenyl phenylacetate
CAS No.	120-24-1
Remarks for Substance	Data for phenylacetic acid ester, isoeugenol phenylacetate. Based on anticipated hydrolysis of ester, phenylacetic acid is formed in vivo. Phenylacetic acid is the predominant metabolite of phenethyl alcohol
Method/guideline	Micronucleus test
Test Type	Clastogenic assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	564, 987, or 1,410 mg/kg bw in olive oil
Exposure Period	Two doses at 0 and 24 hours
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 564, 987, or 1,410 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976). The intraperitoneal LD50= >1500 mg/kg. Positive control as specified in previous publication (Eckhardt et al., 1980).
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 335, 670, and 1,005 mg/kg bw was 2.3, 1.3, 2.5, and 3.0, respectively.
Genotoxic effects	None
Conclusion Remarks	Phenylacetic acid, isoeugenol ester, did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. The data were acquired by standard methodology and published in a peer-reviewed journal but there was a limited description of the protocol and the results were tabulated.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

4.3 Repeated Dose Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Method/guideline	Oral subchronic study
GLP	No
Year	1981
Species/strain	Rat
Sex	Male
Route of Administration	Oral-Gavage
Doses/concentration Levels	51 mg/kg bw/day
Exposure Period	4 months
Frequency of Treatment	Daily
Remarks for test conditions	Only liver function tests were conducted.
Control Group	Untreated
Post Exposure	None
Toxic Response/effects by Dose Level	Evidence of enzyme induction seen
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods.
References	Zaitsev A. N. and Rakhmanina N. L. (1974) Some data on the toxic properties of phenylethyl and cinnamyl alcohols. Voprosy pitaniia, 6, 48-53.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Data given for homologue phenethyl phenylacetate
Method/guideline	Oral subchronic study
GLP	No
Year	1967
Species/strain	Rat/Osborne Mendel

Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0, 1,000, 2,500 or 10,000 ppm approximately an average daily intake of 0, 50, 125, or 500 mg/kg bw.
Exposure Period	17 weeks
Frequency of Treatment	Daily
Control Group	Untreated diet
Post Exposure	None
Remarks for Test Conditions	Groups of ten male and ten female Osborne-Mendel rats were provided phenethyl phenylacetate in the diet at concentrations of 0, 1,000, 2,500 or 10,000 ppm which corresponds to an average daily intake of 0, 50, 125, or 500 mg/kg bw per day for 17 weeks. Measurements of body weight and food intake were recorded weekly.
NOAEL (NOEL)	10,000 ppm or 500 mg/kg bw
LOAEL (LOEL)	None
Actual dose received by dose level and sex	Not reported
Toxic Response/effects by Dose Level	No effects at any dose
Statistical Evaluation	Not given
Remarks for results	Measurement of body weight and food intake recorded weekly showed no significant difference between test and control animals at any intake level. At termination, hematological examinations revealed no effects due to administration of the test substance. At necropsy, no differences were reported in major organ weights between test and control animals including the liver, kidneys, spleen, heart and testes. Gross examination of tissue of all animals was unremarkable and histopathological examination of six-eight animals, equally represented by gender, for the high-dose group and the control group revealed no treatment-related lesions for tissues prepared from the above mentioned organs.
Conclusion remarks	The NOAEL was determined to be greater than 500 mg/kg bw/d.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hagan E. C., Hansen W. H., Fitzhugh O. G., Jenner P. M., Jones W. I., Taylor J. M., Long E. L., Nelson A. A. and Brouwer J. B. (1967) Food Flavourings and Compounds of related Structure. II. Subacute and Chronic Toxicity. Food and Cosmetic Toxicology, 5, 141-157.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Test substance was administered as a mixture and included 6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%).
Method/Guideline	Oral subchronic study
GLP	No
Year	1969
Species/strain	Rats/Wistar
Sex	Male and Female
Route of Administration	Oral-drinking water
Doses/concentration Levels	6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%)
Exposure Period	56 weeks
Frequency of Treatment	Daily
Control Group	Yes, tap water only
Post Exposure	None
Remarks for Test Conditions	Groups of male and female Wistar albino rats (20/sex/group) were given a mixture of compounds dissolved in tap water as their only drinking source for 56 weeks. This mixture included 6,000 mg/kg bw ethyl alcohol (6%), 4 mg/kg bw ethyl acetate (0.004%), 120 mg/kg bw isoamyl alcohol (0.12%), 120 mg/kg bw phenethyl alcohol (0.12%), 200 mg/kg bw isobutyl alcohol (0.2%), and 200 mg/kg bw acetic acid (0.2%). A control group of 20 rats/sex was maintained on tap water only. Body weights were recorded weekly. The activity of alcohol dehydrogenase (ADH), glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and the protein content were determined at two-four week intervals in the livers of rats. At study termination, liver, kidney, heart, spleen, and lung were examined histologically.
Toxic Response/effects by Dose Level	There was a slight non-statistically significant decrease in the mean body weight of the test groups at 28-29 weeks compared to 53-56 weeks. There was no difference in absolute or relative liver weight between the test and control groups. There was a slight increase in GOT activity between 28 and 56 weeks in the test and control groups. No significant abnormalities were

	observed in any of the organs examined. Six animals contracted pneumonia and were discarded. Pneumonia was common in the rats at termination, equally distributed in all groups. The authors concluded that the mixture of chemicals tested did not produce any effects in the parameters tested.
Statistical Evaluation	Yes, Kruskal-Wallis test
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods.
References	Johannsen E. and Purchase I.F.H. (1969) Kaffircorn malting and brewing studies. XXI: The effect of the fusel oils of Bantu beer on rat liver. S.A. Medical Journal (Supplement- S.A. Journal of Nutrition, 43(12), 326-328.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 99.8%
Method/Guideline	Subchronic study-sex organ analysis
GLP	Ambiguous
Year	1981
Species/strain	Rat/Charles River CD
Sex	Male and Female
Route of Administration	Dermal
Doses/concentration Levels	0.25, 0.5, 1.0 & 2.0 ml/kg bw/day
Exposure Period	90 days
Frequency of Treatment	Daily
Control Group	Untreated
Post Exposure	None
Remarks for Test Conditions	Groups of Charles River CD albino rats (5M & 5F) 6-8 weeks of age were administered 0.25, 0.5, 1.0 and 2.0 ml/kg bw/d for 90 days. Material applied to the shaved dorsal. Animals were observed daily for appearance and behaviour changes. Parameters evaluated weekly-included weight gain, food intake. Funduscopic and biomicroscopic examinations were performed on the eyes of all animals. Biochemical analyses were performed for serum glucose, BUN, ALP, ASAT, and ALAT. Urine samples were collected at weeks 6 and 13 and analyzed for volume, specific gravity, ordor, bilirubin, occult blood, protein glucose and ketones. At necropsy, brains, kidneys, liver, and gonads were weighed. Histopathologic examination was

	performed on the adrenals, brain, heart, kidneys, liver, lung, mesenteric lymph node, pituitary, sternum, spinal cord, testes with epididymides, ovaries, spleen, urinary bladder and nerve with muscle from all control and those at in the highest dose group.
NOAEL(NOEL)	0.5 ml/kg bw/day
LOAEL (LOEL)	1.0 ml/kg bw/day
Toxic Response/effects by Dose Level	All animals survived the test in seemingly good health. Significant decreases in body weight gain and body weights were reported for both sexes at the two highest dose levels. Decreased haemoglobin and white blood cell counts were reported for the high dose males only. Clinical chemistry values revealed normal values for test and control groups. Significant increases ($P<0.05$) in relative brain, kidneys, and gonads (males) were reported for both sexes of rats at the 2 ml/kg dose level. Absolute and relative liver weights were decreased for males at 1.0 ml/kg. The change was not confirmed at the higher dose level and, therefore, thought to be not toxicologically significant. Relative liver weights were increased at all dose levels in females. Absolute liver weights remained unchanged. Therefore, the changes reflected a consistent decrease in body weights, particularly in the two high dose groups. Histopathological examination revealed no evidence of tissue alterations that could be related to administration of the test material. Except for the gonad weight change in the high dose group, no other weight change or histopathological observation of any sex organ or tissue were noted.
Statistical Evaluation	Yes
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards. Published in a peer-reviewed journal.
References	Owston E., Lough R. and Opdyke D.L. (1981) A 90-day study of phenylethyl alcohol in the rat. Fd and Cosmet Toxicol, 19(6), 713-715.

4.4 Reproductive Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 99.8%
Method/Guideline	Subchronic study-sex organ analysis
GLP	Ambiguous
Year	1981
Species/strain	Rat/Charles River CD

Sex	Male and Female
Route of Administration	Dermal
Doses/concentration Levels	0.25, 0.5, 1.0 & 2.0 ml/kg bw/day
Exposure Period	90 days
Frequency of Treatment	Daily
Control Group	Untreated
Post Exposure	None
Remarks for Test Conditions	Groups of Charles River CD albino rats (5M & 5F) 6-8 weeks of age were administered 0.25, 0.5, 1.0 and 2.0 ml/kg bw/d for 90 days. Material applied to the shaved dorsal. Animals were observed daily for appearance and behaviour changes. Parameters evaluated weekly-included weight gain, food intake. Funduscopic and biomicroscopic examinations were performed on the eyes of all animals. Biochemical analyses were performed for serum glucose, BUN, ALP, ASAT, and ALAT. Urine samples were collected at weeks 6 and 13 and analyzed for volume, specific gravity, ordor, bilirubin, occult blood, protein glucose and ketones. At necropsy, brains, kidneys, liver, and gonads were weighed. Histopathologic examination was performed on the adrenals, brain, heart, kidneys, liver, lung, mesenteric lymph node, pituitary, sternum, spinal cord, testes with epididymides, ovaries, spleen, urinary bladder and nerve with muscle from all control and those at in the highest dose group.
NOAEL(NOEL)	0.5 ml/kg bw/day
LOAEL (LOEL)	1.0 ml/kg bw/day
Toxic Response/effects by Dose Level	All animals survived the test in seemingly good health. Significant decreases in body weight gain and body weights were reported for both sexes at the two highest dose levels. Decreased haemoglobin and white blood cell counts were reported for the high dose males only. Clinical chemistry values revealed normal values for test and control groups. Significant increases ($P<0.05$) in relative brain, kidneys, and gonads (males) were reported for both sexes of rats at the 2 ml/kg dose level. Absolute and relative liver weights were decreased for males at 1.0 ml/kg. The change was not confirmed at the higher dose level and, therefore, thought to be not toxicologically significant. Relative liver weights were increased at all dose levels in females. Absolute liver weights remained unchanged. Therefore, the changes reflected a consistent decrease in body weights, particularly in the two high dose groups. Histopathological examination revealed no evidence of tissue alterations that could be related to administration of the test material. Except for the gonad weight change in the high dose group, no other weight change or histopathological observation of any sex organ or tissue were noted.
Statistical Evaluation	Yes

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards. Published in a peer-reviewed journal.
References	Owston E., Lough R. and Opdyke D.L. (1981) A 90-day study of phenylethyl alcohol in the rat. Fd and Cosmet Toxicol, 19(6), 713-715.

Substance Name	Phenylacetic acid
CAS No.	103-82-2
Remarks for Substance	Surrogate data for phenethyl alcohol. Phenylacetic acid is predominant metabolite of phenethyl alcohol present in vivo.
Method/Guideline	A 39-day reproduction/developmental-screening assay in SD rats. GLP Regs. FDA (1987)
Test Type	Reproductive/Developmental Toxicity Study
GLP	Yes
Year	1990
Species/Strain	Rat/Sprague-Dawley
Sex	Female/10/group
Route of Administration	Oral/gavage
Duration of Test	39 days
Doses/Concentration	250, 500 & 1000 mg/kg/day
Premating Exposure period for males	Not reported
Premating Exposure period for females	7 days
Control Group and Treatment	Corn oil vehicle, 5 ml/kg/day
Frequency of Treatment	Daily
Remarks for Test Conditions	Virgin female Sprague-Dawley rats (10/group) were orally administered a vehicle or the test material at 3 dosages for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Study duration was 39 days. Maternal toxicity: Dams observed daily for clinical signs and were monitored for mortality, body weight, body weight gain, and food consumption. On day 25 of gestation dams were necropsied and examined for gross lesions. Reproductive performance was monitored in terms of mating index, fertility index, implantation sites per litter, duration of gestation, gestation index and litter size.
NOAEL(NOEL)	250 mg/kg/d (maternal NOAEL) 500 mg/kg/d (developmental

	NOAEL)
LOAEL(LOEL)	500 mg/kg/d (maternal LOAEL))
Appropriate statistical evaluations	ANOVA followed by Dunnett's test
Remarks for Results	The decreased body weights and food consumption reported at 250 mg/kg bw/d during premating period were not considered adverse. Based on the significant decrease in (P less than 0.05) in pup weight at birth and pup viability in the high-dose group, the NOAEL for the F1 offspring was reported to be 500 mg/kg bw/day.
Parental data and F1 as Appropriate	Maternal changes at 250 mg/kg bw included a statistically significant decrease in body weight and body weight gain that was accompanied by a decrease in food consumption. This authors did not consider this as an adverse effect. At the 500 and 1000 mg/kg bw levels, a significant (P less than 0.05) increase in mortality, clinical symptoms of toxicity, and decreased body weight gain and food consumption were reported. At necropsy gross lesion of the liver and other organs was reported. Mating index was decreased in the 1000 mg/kg bw dose group only. In dams included decreased activity and excess salivation during the pre-gestation period and increased (P less than 0.01) salivation in the high dose group during gestation. Significant (P less than 0.05 to less than 0.01) decreases in body weight and absolute and relative food consumption were measured during the premating period.
Offspring toxicity F1 and F2	Significant (P less than 0.05) decrease in pup viability and body weight occurred in the high dose groups compared to controls. No gross lesions in pups were attributable to administration of the test material.
Conclusion remarks	The NOAEL for maternal toxicity was 250 mg/kg bw/day and the NOAEL for reproductive performance was 250 mg/kg bw/day. The developmental NOAEL was 500 mg/kg/day (see below).
Remarks for Results	
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Vollmuth T.A., Bennett, M.B., Hoberman, A.M. and Christian, M.S. (1995) An Evaluation of Food Flavoring Ingredients Using an In Vivo Reproductive and Developmental Toxicity Screening Test. Teratology, 41(5), 597.

4.5 Developmental/Teratogenicity Toxicity

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Not characterized
Test Type	Fetal developmental study
GLP	No
Year	1983
Species/strain	Rat/Long-Evans
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	20 days
Doses/concentration Levels	0, 4.3, 43 & 430 mg/kg bw/d
Exposure Period	Days 6 - 15 of gestation
Frequency of Treatment	Daily
Control Group and Treatment	Vehicle (water) only
Remarks for Test Conditions	The test material was dosed as an aqueous suspension. 19 rats in control group, 7 in low and mid-dose groups and 5 in high dose.
NOAEL(NOEL) maternal toxicity	43 mg/kg
LOAEL(LOEL) maternal toxicity	430 mg/kg
LOAEL (LOEL) developmental toxicity	430 mg/kg
Actual dose received by dose level and sex	Not given
Maternal data with dose level	"Severe intoxication" at high dose and asymtomatic at 2 lower doses.
Fetal Data with Dose Level	The average birth weight was decreased in the lowest and highest dose groups and the pup size of all treated groups were significantly lower than those of the control group. However, the birth weight of the mid-dose group was greater that that of the control group. Mean litter size was greater in the high dose group (13) than in either the two lower doses (9) or controls (12). Also, embryolethality did not occur in the high dose group but was 18% at 43 mg/kg and 10% at 4.3 mg/kg. The authors

	reported a clear dose related increase in the percentage of malformations in live offspring (100% at the 432 mg/kg level, 93% at 43 mg/kg and 50% at 4.3 mg/kg). Malformations were mainly in ocular malformation, neural tube defects, hydronephrosis and limb defects.
Appropriate statistical evaluations	Yes
Remarks for Results	Dose response evident only on grouping of certain malformations. Often no dose response on individual effects or by grouping related effects.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Mankes R. F., LeFevre R., Bates H. and Abraham R. (1983) Effects of Various Exposure Levels of 2-Phenylethanol on Fetal Development and Survival in Long-Evans Rats. Journal of Toxicology and Environmental Health, 12, 235-244.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 98.5%
Method/Guideline	Modified OECD 414
Test Type	Prenatal developmental
GLP	Yes
Year	1986
Species/strain	CrL:COBS CD (SD) BR
Sex	Female
Route of Administration	Dermal
Duration of Test	21 days
Doses/concentration Levels	140, 430 & 1400 ul/kg (approximately 143, 438, or 1430 mg/kg bw)
Exposure Period	Days 6-15 of pregnancy
Frequency of Treatment	Daily
Control Group and Treatment	Water
Remarks for Test Conditions	Test was conducted according to OECD 414 except dosing was only during the period of organogenesis. The effect of phenethyl alcohol on pregnancy of rats was studied (Palmer *et al*., 1986). Phenethyl alcohol was applied topically at the dose of 0, 0.14, 0.43 or 1.40 ml/kg (approximately 143, 438, or 1430 mg/kg bw) during day 6 to 15 of pregnancy. The doses are

	approximately equal to 0, 140, 430, and 1400 mg/kg bw, respectively, and were chosen so that the intermediate dose was roughly equivalent to the highest dosage used in a previous oral study (Mankes *et al*., 1983). The highest dose was designed to extend the range in case of differential absorption by the dermal route. The animals were killed on day 20 of pregnancy and in utero development assessed by determination of litter values and examination of the fetuses for soft tissue and skeletal changes.
NOAEL(NOEL) maternal toxicity	438 mg/kg
LOAEL(LOEL) maternal toxicity	1430 mg/kg
NOAEL (NOEL) developmental toxicity	143 mg/kg
Actual dose received by dose level and sex	143, 438, or 1430 mg/kg
Maternal data with dose level	1430 mg/kg death of 3/35 and suppression of food intake and growth rate with clinical signs of toxicity.
	No significant effects at lower doses
Fetal Data with Dose Level	1430 mg/kg resorption of 5/23 litters, reductions in litter size and weight. Morphological change in 160/161 fetuses.
	438 mg/kg increased incidence of foetuses with cervical rib bud and defects of thoracic vertebrae
	143 mg/kg, no significant effects.
Appropriate statistical evaluations	Yes
Remarks for Results	Although fetal effects at 438 mg/kg were not considered serious according to the authors, this dose cannot be called a NOAEL.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Palmer A.K., Bottomley, A. M., Ratcliffe, H.E. Clark, R., and John, D. M. (1986) Effect of Phenylethyl Alcohol (PEA) on Pregnancy of the Rat. Huntingdon Research Center. Unpublished report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Purity 99.6%
Test Type	Prenatal developmental dosage-range toxicity study
GLP	Yes
Year	1986

Species/strain	CrL:COBS CD (SD) BR
Sex	Female
Route of Administration	Dermal
Duration of Test	21 days
Doses/concentration Levels	70, 140, 280, 430 & 700 mg/kg
Exposure Period	Days 6-15 of pregnancy
Frequency of Treatment	Daily
Control Group and Treatment	Water
Remarks for Test Conditions	The test was conducted as a follow-up to Palmer, *et al.*, 1986 to better define the fetal and maternal NOAELs.
NOAEL(NOEL) maternal toxicity	Less than 70 mg/kg
LOAEL(LOEL) maternal toxicity	70 mg/kg
NOAEL (NOEL) developmental toxicity	140 mg/kg
Actual dose received by dose level and sex	280 mg/kg
Maternal data with dose level	Signs of dermal irritation were seen in all dosed groups.
Fetal Data with Dose Level	The NOEL for the cervical rib formation seen in Palmer *et al.* 1986 was 430 mg/kg. Other effects including incomplete ossification and decreased fetal body weight possibly as an indirect result of the maternal irritation were seen in all dose groups but were considered reversible effects. The only statistically significant difference from controls in the two lower dose groups was incomplete ossification of the pelvis but with no dose correlation.
Appropriate statistical evaluations	Yes
Conclusion Remarks	The study was compromised due to the dermal irritation seen at all dose levels.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Christian M.S. and Hoberman A.M. (1988) Dosage-range developmental toxicity (embryo/fetal toxicity and teratogenicity) study of 2-phenylethylalcohol (PEA) administered dermally to presumed pregnant mice. Unpublished report to RIFM

Substance Name	Phenylacetic acid
CAS No.	103-82-2
Remarks for Substance	Surrogate data for phenethyl alcohol. Phenylacetic acid is predominant metabolite of phenethyl alcohol present in vivo.
Method/Guideline	A 39 day reproduction/developmental screening assay in SD rats. GLP Regs. FDA (1987)
Test Type	Virgin female Sprague-Dawley rats (10/group) were orally administered a vehicle or the test material at 3 dosages for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Study duration was 39 days.
GLP	Yes
Year	1990
Species/strain	Rat/Sprague-Dawley
Sex	Female/10/group
Route of Administration	Oral-Gavage
Duration of Test	39 days
Doses/concentration Levels	250, 500 & 1000 mg/kg/day
Exposure Period	7 days premating, through gestation and 4 days postpartum (39 days)
Frequency of Treatment	Daily
Control Group and Treatment	Corn oil vehicle, 5 ml/kg/day
Remarks for Test Conditions	Virgin female Sprague-Dawley rats (10/group) were orally administered a vehicle or the test material at 3 dosages for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Study duration was 39 days. Developmental toxicity was monitored in terms of mortality, viability (pups dying on days 1-4), pup body weight and pup body weight gain.
NOAEL(NOEL) maternal toxicity	250 mg/kg bw
LOAEL(LOEL) maternal toxicity	500 mg/kg bw
NOAEL (NOEL) developmental toxicity	500 mg/kg bw
LOAEL(LOEL) developmental toxicity	1000 mg/kg bw

Maternal data with dose level	Maternal changes at 250 mg/kg bw included a statistically significant decrease in body weight and body weight gain that was accompanied by a decrease in food consumption. At the 500 and 1000 mg/kg bw levels, a significant (P less than 0.05) increase in mortality, clinical symptoms of toxicity, and decreased body weight gain and food consumption (P less than 0.05) were reported. At necropsy gross lesions of the liver and other organs were reported. Mating index was decreased in the 1000 mg/kg bw dose group only. Effects in dams included decreased activity and excess salivation during the pre-gestation period and increased (P less than 0.01) salivation in the high dose group during gestation. Significant (P less than 0.05 to less than 0.01) decreases in body weight and absolute and relative food consumption were measured during the premating period.
Fetal Data with Dose Level	No effects on development were observed at 250 or 500 mg/kg bw. Offspring effects observed only at the highest dose included a statistically significant (P less than 0.05) decrease in viability and a non-significant decrease in body weight gain.
Appropriate statistical evaluations	ANOVA followed by Dunnett's test
Remarks for Results	The decreased body weights and food consumption reported at 250 mg/kg bw/d during premating period were not considered adverse. Based on the significant decrease in (P less than 0.05) in pup viability in the high-dose group, the NOAEL for the F1 offspring was reported to be 500 mg/kg bw/day.
Conclusion Remarks	The NOAEL for development of offspring is 500 mg/kg bw/day.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Vollmuth T.A., Bennett, M.B., Hoberman, A.M. and Christian, M.S. (1995) An Evaluation of Food Flavoring Ingredients Using an In Vivo Reproductive and Developmental Toxicity Screening Test. Teratology 41(5), 597.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Remarks for Substance	Blended commercial sample, purity 98.5%, from 4 manufacturers spray dried with gum Arabic at a concentration of 17.6%.
Method/Guideline	Essentially the same as OECD 414 except dosing was on days 6 – 16 of pregnancy.
Test Type	Prenatal Developmental Toxicity Study
GLP	Yes
Year	1987

Species/strain	CrL: COBS CD(SD)BR rats
Sex	Female
Route of Administration	Oral-Diet
Duration of Test	20 days
Doses/concentration Levels	0, 1000, 3000 & 5000 ppm resulting in intakes of about 83, 266 & 799 mg/kg/day.
Exposure Period	Days 6-15 of pregnancy
Frequency of Treatment	Daily
Control Group and Treatment	Gum Arabic
Remarks for Test Conditions	Microencapsulation in Gum Arabic was used to prevent decreased food intake due to in appetence. Bioavailability was demonstrated in separate study (Hawkins *et al*., 1990).
NOAEL(NOEL) maternal toxicity	5000 ppm
LOAEL(LOEL) maternal toxicity	None
NOAEL (NOEL) developmental toxicity	5000 ppm
LOAEL(LOEL) developmental toxicity	None
Actual dose received by dose level and sex	Mean daily intakes during days of dosing were 83.1, 265.9 & 799.1 mg/kg.
Maternal data with dose level	No effects at any dose.
Fetal Data with Dose Level	No effects at any dose.
Appropriate statistical evaluations	Yes
Remarks for Results	The study was conducted to determine the effect of route of dosing on developmental toxicity.
Conclusion Remarks	There was no evidence of maternal or fetal toxicity at any dose level after dietary administration.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Bottomley A. M., Ratcliffe H. E., John D. M., Anderson A., Dawe I. S. (1987) Effect of Dietary Administration of Micro-Encapsulated Phenylethyl Alcohol on Pregnancy of the Rat (Embryotoxicity Study). Unpublished Report to RIFM.

Substance Name	Phenethyl alcohol
CAS No.	60-12-8
Test Type	Embryotoxicity
GLP	No
Year	1973
Species/strain	Rats/Mongrel white
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	20 days
Doses/concentration Levels	508 mg/kg
Exposure Period	Once on 4th day of pregnancy or once during 10-12th day.
Frequency of Treatment	Once
Control Group and Treatment	Solvent only
Remarks for Test Conditions	Administered in sunflower oil.
Actual Dose Received by Dose Level and Sex	508 mg/kg
Maternal data with Dose Level	No maternal data reported
Fetal Data with Dose Level	Single dose level of 508 mg/kg caused no effects when administered at the 4th day of pregnancy but caused slight retardation of ossification when administered during the 10-12th day.
Appropriate Statistical Evaluations	Not reported
Remarks for Results	While study is poorly reported, results are consistent with other studies.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Method not validated.
References	Maganova N.B. and Zaitsev A.N. (1973) Study of the Embryotoxic Action of Some Synthetic Food Flavourings. Vopr Pitan, 32(4), 50-54.